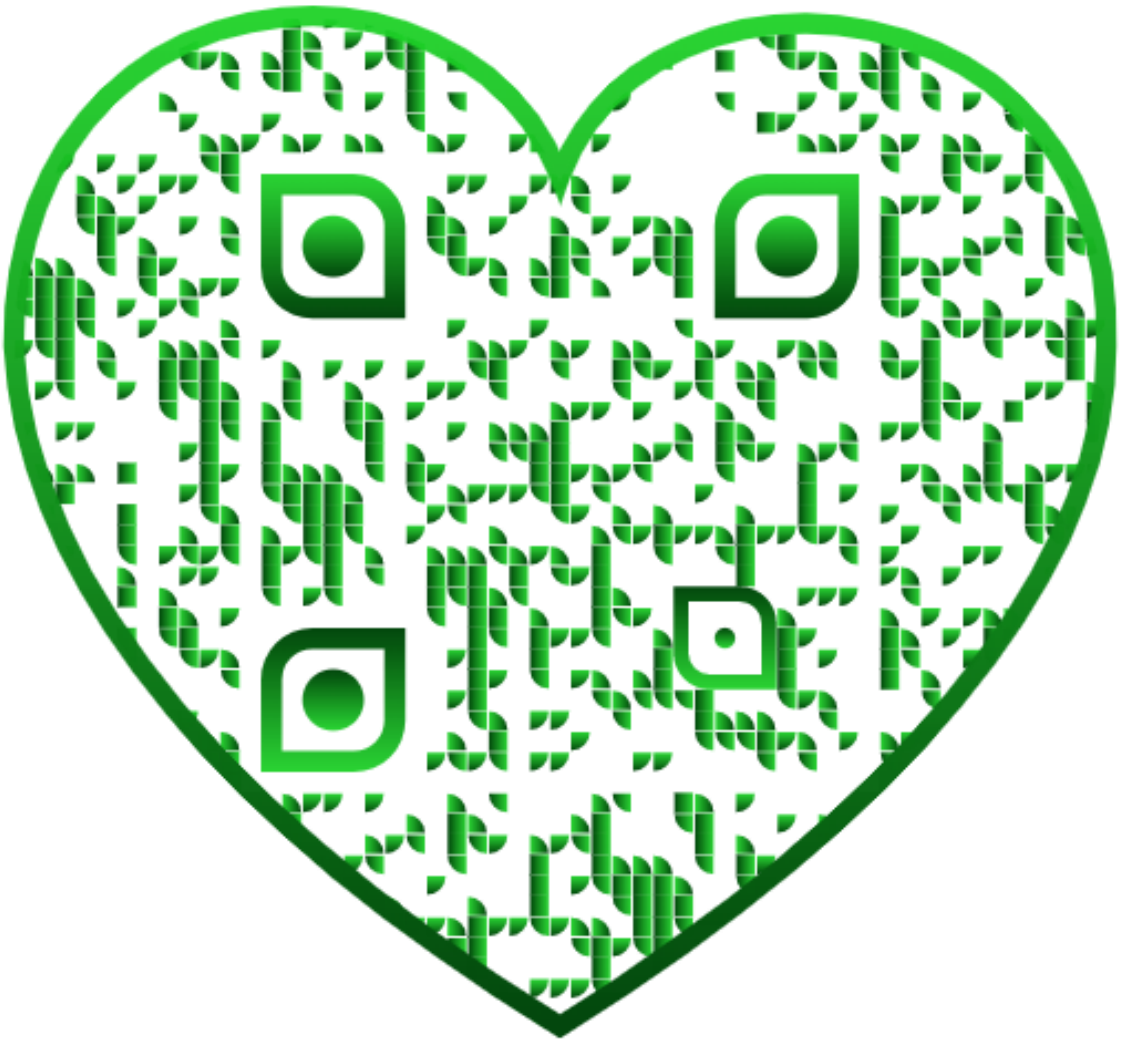
2. Suppositories and Pessaries



Introduction

- Physiology of Rectum and Vaginal cavity, and rectal and Vaginal drug delivery
- Challenges of Drug Delivery through vagina and rectum
- Methods of enhancing drug absorption

Physiology of Rectum and Rectal drug delivery

- Oral route is the preferred route for drug delivery,
- But, this route may not be practical or feasible when:
  - Patient has nausea, vomiting or convulsion
  - Patient is uncooperative
  - Oral route is restricted

- The rectal route can be used effectively to treat local conditions and to deliver drugs systemically
  - Treating certain rectal conditions may be best achieved by localized drug administration at or near the affected area.
- Rectum is terminal part of the large intestine
  - 12-19 cm long
  - Surface area of 200-400 cm^2
  - Containing small amount of fluid

- The anus connects the rectum to the outside of the body, and the anal canal is about 4 cm long
  - Drugs applied to the anal canal and up to the anorectal line are not absorbed systemically
    - Because the skin like tissue of the anal canal serves as a barrier
    - Agents applied to this region have primarily a local action

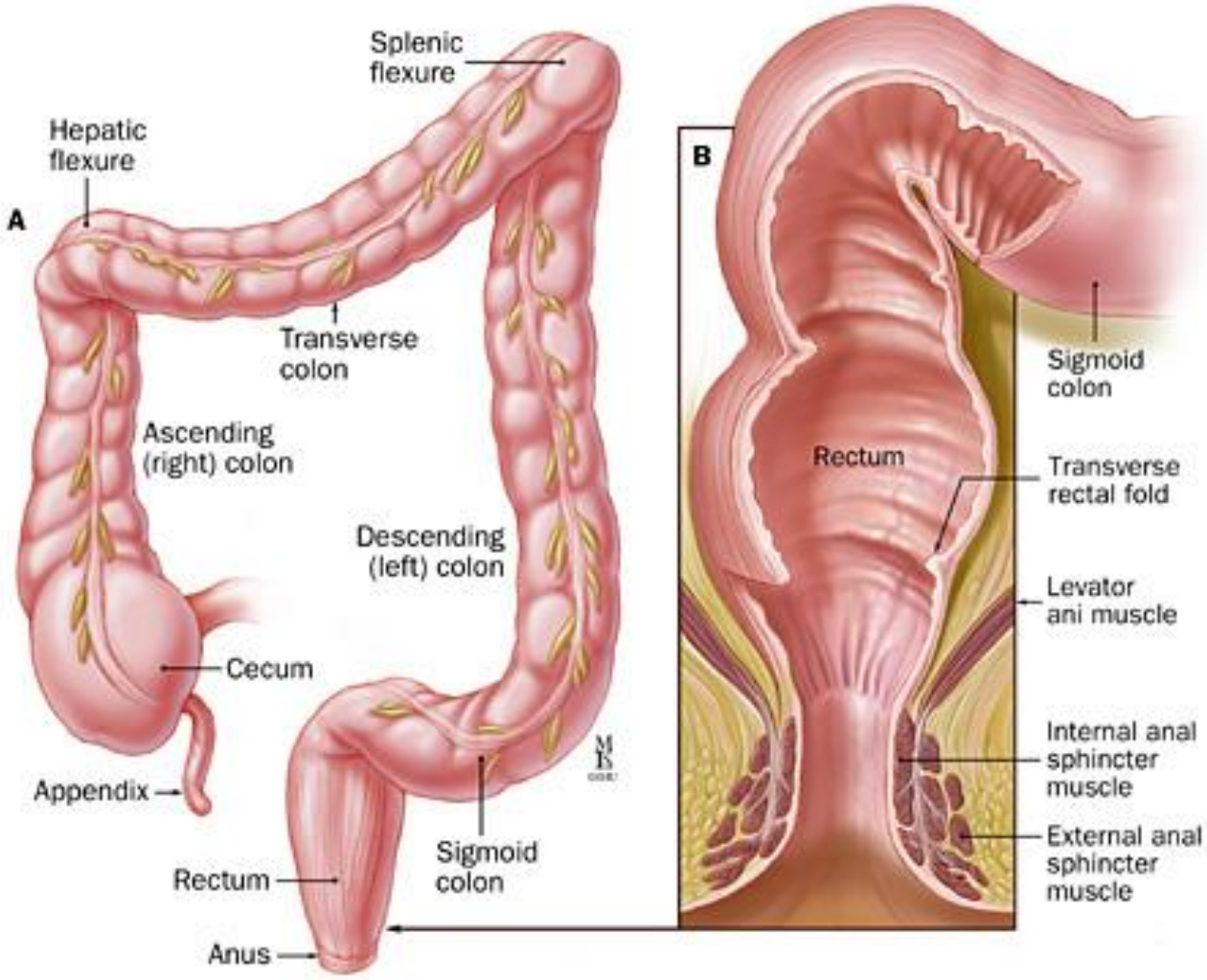


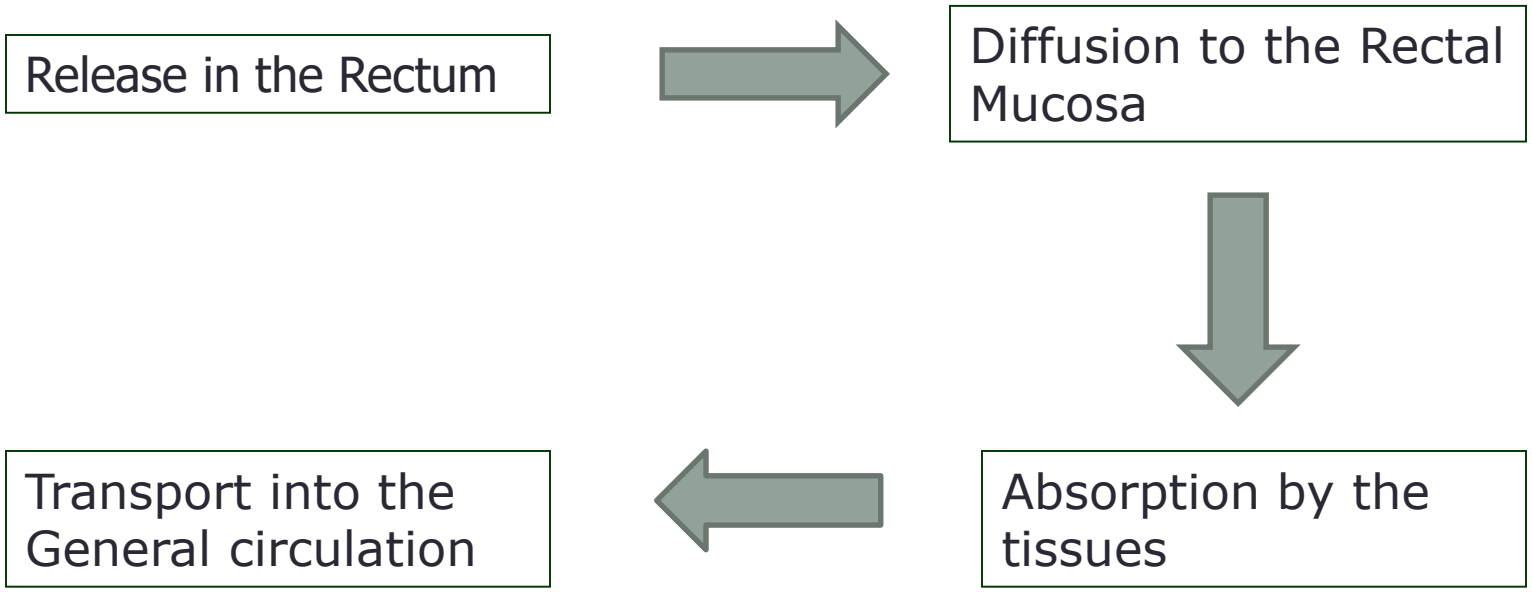
Fig. Rectal anatomy

- Rectal epithelium is vascularized,
  - The inferior and middle hemorrhoidal or rectal veins from the lower rectum drains directly into the systemic circulation.
    - Therefore, drugs absorbed from the lower rectum do not under go first-pass metabolism.
  - The superior hemorrhoidal or rectal veins from the upper rectum drains directly in to the portal circulation.
    - Drugs from the upper rectum are carried directly to the liver.

- The main mechanism of drug absorption from rectal delivery is passive diffusion
  - Absorption mainly depends on:
    - Drug molecular weight
    - Lipid solubility, and
    - Degree of ionization

- The pH of the rectal fluids and rectal contents show a wider range, and this could be the reason for the wide variation in bioavailability of drugs.
- Adult rectal pH is about 7.2, which varies depending on the rectal contents.
- In children, higher range of pH is recorded (7.2 – 12.1).

- Absorption of systematically active drug from rectal deliver systems follows different stages;


Release in the Rectum
Diffusion to the Rectal Mucosa
Absorption by the tissues
Transport into the General circulation

- Different factors influence rectal absorption of drugs:
  - Partition coefficient of drug
  - PH of rectal secretions
  - Physical state of medicament
  - Presence of adjuncts in the base
- The formulation characteristics play a significant role in drug absorption

- Rate limiting factor in rectal absorption appears to be the rate at which the drug diffuse to the rectal mucosa.
- The concentration of the drug in suppository base is essential to get a higher blood concentration of the drug,
  - In a rectal drug delivery, often, a dose 50 to 200 % more than the oral dose must be administered to obtain adequate response.

- Advantages of rectal drug delivery:
  - Its relatively painless and convenient to use (Pediatric and geriatric patients).
  - Useful for local action (a high concentration of a drug can be achieved)
  - Will avoid first-pass effect
    - If administered low in the rectum absorption will occur to the inferior and middle rectal veins

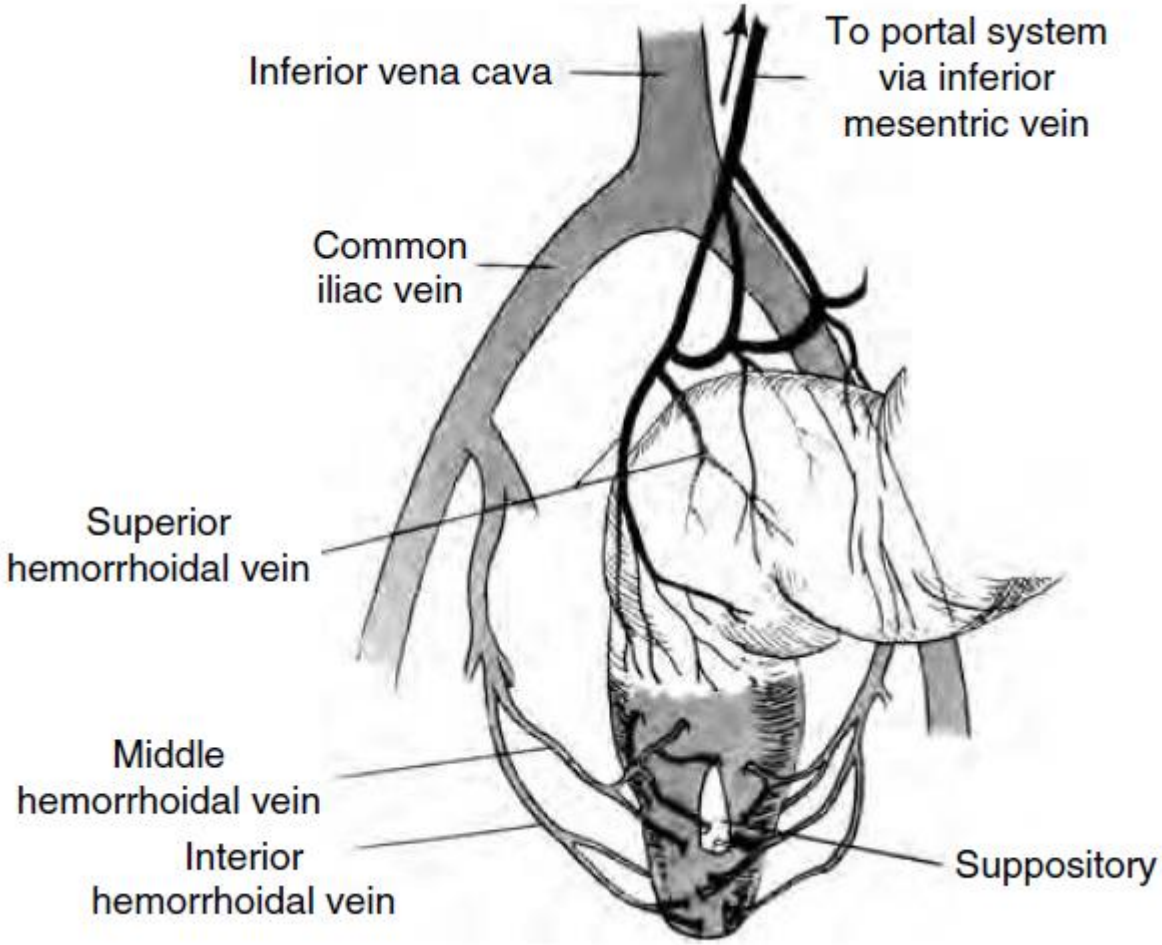


Fig. Major blood vessels of the rectum and proper position of the suppository.

- Disadvantages of rectal drug delivery:
  - Inter- and intra-subject variability in drug absorption
  - Presence of diarrhea and other diseases
  - Patient compliance issues
  - Mucosal irritation from some drugs

Physiology of Vagina and Vaginal drug delivery

- The vagina is S-shaped fibro-muscular tube of 2 cm wide and 6-10 cm long.
- Vaginal mucosa contains epithelium, which consists of non-keratinized and stratified squamous cells, and loose connective tissue.
  - It is more similar to the buccal mucosa
  - It is covered with thin film of viginal fluid
  - Highly vascularized

- Thickness of the epithelium varies with age and hormonal activity
- Vaginal pH ranges 3.5 – 4.5 (reproductive age), this pH is maintained by lactobacili, which convert hydrogen to lactic acid
  - pH ranges from neutral to slightly basic for postmenopausal women, and girls not reached in puberty.
  - The pH also varies with: menstrual cycle, presence of semen, during infection

- Ionization of weakly acidic and basic drugs are altered by changes in pH.
- Vagina has a SA of 60 cm^2.
  - This large SA with the high vasculature enable rapid absorption of low molecular weight drugs.
- Extent of drug absorption from vaginal drug delivery systems depend on: Residence time, Dosage form, and Contact time of the drug with the epithelium

- Vaginal drug delivery systems such as solutions, foams, gels, and tablets are removed relatively rapidly
  - The contact time increases if the drug is delivered in a ring or along with mucoadhesive or bioadhesive gel
- For lipophilic drugs, drug permeation is primarily by passive diffusion
  - For hydrophillic and ionized drug, permeation is via paracellular route

- Vaginal, uterine, vesical, and retrosigmoid veins from the middle and upper vagina drains into the inferior vena cava.
- The vaginal cavity contains a small amount of fluid (2-3 ml)
  - Dissolution of drug can be the rate limiting step for systemic absorption and is of particular importance for poorly soluble drugs.
- Some enzymatic activities from the vaginal epithelium could result in deactivation of some drugs.

- Advantages of vaginal drug delivery:
  - The rich vasculature of the mucosa makes this route attractive for systemic delivery of drugs.
  - The delivery system can be localized on the vaginal mucosa for many hours without causing a pronounced irritation.
  - Intravaginal enzymatic activity is comparatively lower in the vagina than in the GIT.
  - First-pass hepatic metabolism is avoided.
  - Convenience of self-administration.
  - Painless

- Disadvantages of vaginal drug delivery:
  - Thickness of vaginal epithelium and the pH vary with age, hormonal activity and the menstrual cycle
    - This affects the permeability of the drug and hence the extent of absorption
  - Systemic absorption of drug can be erratic and unpredictable
  - The formulation may leak or slip out (especially solution, gels, and semisolids)
  - Drugs or other ingredients may cause local irritation

Challenges of Drug Delivery through vagina and rectum

- Drug solubility, concentration, and particle size; presence of mucus; and surface area affect bioavailability from the rectum and vagina.
- An uncooperative patient could expel the product.
- Suppositories may tend to migrate after insertion.
- Incompatibility issues.
- Excessive softening of suppositories

- Different factors also influence rectal/vaginal absorption of drugs:
  - Partition coefficient of drug
  - PH of rectal secretions
  - Physical state of medicament
  - Presence of adjuncts in the base

Suppositories

- Definition
- Selection of suppository bases
- Preparation of Suppositories
- Packaging and Storage of Suppositories

Definition

- Suppositories are conical or ovoid, solid preparations for insertion in to the rectum where they melt dissolve or disperse and exert a local or less often, a systemic effect.

- The word suppository comes from the Latin word ‘supponere’, meaning “to place under”

- They are the most commonly used rectal and vaginal solid dosage forms.

- The pharmaceutical need for suppositories:
  - To exert a direct action on the rectum
    - To relieve the pain & irritation of hemorrhoids; Local anesthetics, Astringents, and Anti-inflammatory agents may be administered.
  - To promote evacuation of the bowel
  - To provide systemic effect
    - For patients who are – Unconscious, Mentally disturbed, Unable to tolerate oral medication
    - For drug that cause gastric irritation
    - For infants

- Commonly used suppository shapes & sizes
  - 1g - suppository
    - Cone shaped with a round apex (bullet –shaped)
  - 2g – suppository
    - The same shape as the 1g suppository
- The pointed apex part of the suppository is of practical importance
  - When the widest part has been inserted, the anal sphincter muscle passes the suppository forward into the rectum.
  - It facilitates insertion and retention in the rectal cavity.

Suppository Bases

- The suppository base employed has a marked influence on the release of active constituents incorporated into it.
- Selection of a suppository base is greatly influenced by the physicochemical properties of drug and desired drug release pattern
- The ideal suppository base should have following properties:
  - Nontoxic and nonirritating to the mucous membrane
  - Compatible with a variety of drugs

- Should melting / dissolving in rectal fluids
- Should release any medicament readily
- Should keep its shape when being handled
- Should be easily molded & not adhere to the mold
- Should be moldable by pouring or cold compression
- Should be heat stable
- Should be stable on storage
- Should not bind or otherwise interfere with the release and absorption of drug substances

- The bioavailability of a drug from the suppository dosage form is dependent on the physicochemical properties of the drug as well as the composition of the base.

- Relative solubility of the drug in the vehicle used to formulate the base is an important measure

  - E.g. Drugs that are only slightly soluble in the lipid base partition readily into the rectal fluid.

- Suppository bases are classified on the basis of their physical characteristics into three main categories:

    1. Fatty or oleaginous bases

    2. Water-miscible or water-soluble bases

    3. Miscellaneous bases

1. Fatty or Oleaginous Bases

- These are the most frequently used suppository bases.
- Are solid at room temperature but melt quickly at body temperature
- Commonly used Oleaginous bases include: Theobroma Oil (Cocoa Butter), Synthetic fats and hydrogenated vegetable oil bases
- Fat based compounds containing compounds of glycerin with high molecular weight fatty acids are used to achieve the desired melting point and hardness to withstand shipping.

A. Theobroma Oil (Cocoa Butter)

- Theobroma oil (TBO) is the only natural fat with suitable properties for suppositories
- Yellowish white solid with chocolate like odor
- It is a mixture of the glyceryl esters of fatty acids (like stearic, palmitic and oleic acids)
- It has 4 different polymorphic forms: α, β, β', and Υ with MP of 22, 34-35, 28, and 18 ^{o}C respectively
- Lowering of the M.P of the base may lead to sedimentation of suspended solids, and over heating should be avoided during preparation

- The β form is the most stable and desired form
  - When heated to a temperature higher than 36-40 ^{o}C, and then rapidly cooled, it will result in a metastable α-form.
- Polymorphs with lower M.P eventually will convert to the more stable form over time.
  - Maintaining careful temperature control during the preparation of cocoa base based suppositories is extremely important.

Advantages of TBO

- Its M.P ranges from 30 – 36 ^{o}C
- Solid at room temperature, but melt at body temperature
- Ready liquefaction on warming and rapid setting on cooling
- Miscibility with many ingredients
- Blandness

Disadvantages of TBO

- Polymorphism
  - When melted and cooled it solidifies in different crystalline forms, depending on the temp of meeting, rate of cooling, and size the mass
- Adherence to mold
  - It dose not contract enough on cooling to loosen the suppositories in the mold (lubricate the mold before preparation)
- Deterioration on storage due to oxidation of the unsaturated glycerides

- Softening point too low for hot climates,
  - White beeswax may be included for use in tropical & subtropical countries
  - Only 4-5% white bees wax is sufficient. The more white bees wax, the suppository may not melt at body temperature.
- Its M.P reduced by soluble ingredients
- Leakage from the body
  - The melted base may escape from the rectum or vagina
- Relatively costly

B. Synthetic fats

- Synthetic substitutes which are free from disadvantage of TBO are necessary.
  - Hydrogenation and subsequent heat treatment of vegetable oils (Palm Kernel Oil & Arachis oil), OR
  - **Hydrolyzing** vegetable oils, and then **hydrogenating** the resulting fatty acid, & finally **re-esterifying** the acids.

Advantages of synthetic fats

- Their solidifying points are unaffected by overheating
- They have good resistance to oxidation, because the unsaturated FAs have been reduced
- The difference between M.P and setting points is small, therefore it can set quickly
  - Rate of sedimentation is low
  - Easier to administer

NB: When the setting point of a base is well below the M.P, the suppository soften quickly & become slippery to administer.

- Different grades with slightly different M.P ranges are available
- Emulsifying & water absorbing capacity is good
  - They contain a proportion of partial glycerides (e.g. glyceryl monostearate)
- Contract significantly on cooling, therefore no mold lubricant is necessary
- Their suppositories are white & almost odorless

Disadvantages of synthetic fats:

- Become brittle if cooled quickly
  - Not to be cooled in a refrigerator or ice box
  - Some additives may be included to solve this drawback (e.g. Polysorbate 80)
- They are more fluidic than TBO when melted
  - Thickeners may be included to solve this problem, e.g. Mg-stearate, Bentonite & Colloidal Silicate.

C. Hydrogenated vegetable oil bases

- These are mixtures of fatty acids and cotton seed oil
- Unsaturated vegetable oils can be transformed through **partial** or **complete hydrogenation** into oils of higher M.P.
  - Vegetable oils are generally liquid at room temperature
  - The advantage of hydrogenation of vegetable oils is that it gives a uniform product that is solid at room temperature and has a long shelf life.
- There is no polymorphic problem

2. Water-Miscible and Water-Soluble Bases

- These base do not melt at body temperature, but dissolve slowly in the fluids.

Water-Miscible Bases

- E.g. Glycerinated gelatin bases (Glycero-Gelatin bases)
- Glycerinated gelatin bases are made by dissolving gelatin in glycerin.
- They are more slower to soften and mix with the physiologic fluids than is TBO, and therefore, provides a slower release.

- May be used for jellies, suppositories or pessaries, where **proportions** being adjusted depending on the purpose
  - E.g. For Suppositories and Pessaries: 14 % (w/w) gelatin + 70 % (w/w) glycerol
- Glycero-gelatin bases are most commonly used in preparation of pessaries, where the prolonged localized action is desired.
- To increase stiffness for hot climates 18 % gelatin may be used
- The proportion of gelatin may be increased if the product contains more than 20 % of a semi-solid or liquid

Drawbacks of Glycero-gelatin bases

- They posses some physiological actions
- They are more difficult to prepare & handle
- Their dissolution time depends on content & quality of the gelatin & age of the base
- They are hygroscopic; this in turn will cause spoilage of the product on storage and dehydration of rectal mucosa
- Gelatin is incompatible with protein precipitants (e.g. Tannic acid) and some production impurities

- Drugs (cationic or anionic) should not be formulated with gelatin of opposite charge.

- Drugs which will be precipitated by acids should not be compounded with type A gelatin (and vice-versa)

Water-Soluble Bases

E.g. PEGs (Macrogols)

- May be liquids or solids depending on the molecular weight

- Wide range in molecular weight (PEG 300 to PEG 8000), so a single or combination of PEGs could be used to prepare a suppository base of desired consistency and characteristics

Advantages of PEGs

- PEG suppositories do not melt at body temperature, but dissolve slowly in body fluids (generally have a M.P above 42 ^{O}C);

  *Enable slower release of the drug on insertion into the rectum.

  *Need not be refrigerated.

  *They might be inserted slowly into the body.

  *Do not leak from the orifice.

- Physical properties can be varied by suitable admixture of high & low polymers
- Don’t stick to the mold (unlike glycero-gelatin bases),
- They absorb water well, and show excellent solvent property

Drawbacks of PEG

- PEGs are hydroscopic
- PEGs may reduce therapeutic activity of the API/drug
- Product may fracture on storage
- Crystal growth of certain drugs may occur
- Incompatibility problems

3. Miscellaneous Bases

- Mixtures of lipid and water-soluble bases, and some macromolecular polymers may also be used as suppository bases.

- E.g. **Polyoxyl 40 stearate**, which is a mixture of monostearate and distearate esters of mixed polyoxyethylene diols and the free glycols

  Hydrogels (macromolecular networks that swell but do not dissolve)

  - Hydrogels are potential for controlled drug delivery, bioadhesion, retention at the site of administration, and biocompatibility

Preparation of Suppositories

- Suppositories are prepared by three methods:
  - Molding
  - Compression, and
  - Hand rolling and shaping

A. Molding

- The most commonly used method for producing suppositories on both a small and large scale is the molding process

- The steps in molding include:

  a) Melting the base,

  b) Incorporating required medicaments,

  c) Pouring the melt into molds, and

  d) Allowing the melt to cool and congeal into suppositories and removing the formed suppositories from the mold.

- The molds in common use today are made from stainless steel, aluminum, brass, and plastic.
- Molds are of various capacities, depending upon the scale of production.
  - Common molds have a capacity of 1g, 2g, 4g or 8g
  - For common dispensing two kinds of molds are used: molds of 6 cavities and molds of 12 cavities
- Molds are opened longitudinally for cleaning before and after preparation of suppositories.
- Care must be taken while cleaning molds, as scratches may affect the desired smoothness of the final product.

1. Lubrication of the Mold

- This is an important step in the preparation of suppositories.
- Lubrication is required for **clean and easy removal** of suppositories.
- Bases that contract significantly on cooling seldom require lubrication.
- Lubrication is necessary when glycerinated gelatin suppositories are prepared.
    - A lubricant must differ in composition from the suppository bases.

- Lubricant may be applied on a pads of gauze or muslin, or with small fairly stiff brush, and avoid cotton wool because the fibers detach too easily.

- Avoid excessive lubrication.

  - Drops on the side and bottom of the cavities could cause depression in the product.

2. Calibration of the Mold

- The normal capacity of a mold will vary for different bases
- It is necessary to account for different densities of different bases.
  - For instance, the weight of suppositories prepared from TBO differs from that of PEG for a particular mold
- Furthermore, any added medicinal agent alters the density and hence the weight of the resulting suppository.

- Therefore, the mold should be calibrated before use, i.e., allowance must be made for the change in density of the mass because of added drug
  - And to do this we calculate 'Displacement Values'
  - Empty suppositories are prepared from base material alone
  - The suppositories are weighed and their volume is determined by melting.
  - Thus the density is computed for that particular base.
  - Record the values for future use

- In the case of extemporaneous preparations;
  - We may need to determine the amount of the base required to be incorporated along with the medicaments, so that each suppository provides the required amount of the drug
  - The volume of the base required is determined by subtracting the volume of the medicaments from the total volume of the mold
  - The density of the material is used to calculate the volume of the base required

E.g. If 12 ml of TBO is required to fill a mold, and if the volume of the medicaments is 3.4 ml, then the volume of the TBO required is 8.6 ml.

The weight of the base required is then obtained by multiplying the density of TBO (0.86 g/ml) with 8.6 ml, which is 7.4 g.

3. Preparing and Pouring the Melt

- The weighed base is melted over a water bath by using the least possible heat.
- Medicaments are usually incorporated into a portion of the melted base by mixing on a porcelain or glass tile with a spatula.
- This material is then added with stirring to the remaining base, which is cooled almost to its congealing point.
- Any volatile or thermolabile substances should be added to the base with thorough stirring at this point.
- This material is now poured carefully and continuously into the chilled mold.

- If any undissolved solid materials with a tendency to settle are present, the material should be poured with constant stirring.
- The chilled mold avoids settling of the solids within the mold and also aids in congealing.
- If the melt is not at the congealing point when poured into the cavities, the solids may settle within each cavity of the mold,
  - This will cause inaccurate distribution of the active ingredient in the bulk of the suppository.
- Filling of the suppository cavity should be continuous to avoid layering, which may lead to a product that is easily broken when handled.

- To ensure complete filling of the mold upon congealing, the melt is poured above the level of the mold over each opening.
- After solidification the excess material is scrapped off.
- The mold is then kept in the freezer to promote hardening of the suppositories
- When the suppositories are hard, the mold is removed from the freezer, the sections of the mold are separated, and the suppositories are removed, with pressure being exerted at the ends.

B. Compression

- Suppositories are made by forcing the mixture of the suppository base and the medicaments into special molds using suppository making machines.

- The suppository base and the medicaments are combined by thorough mixing, and the heat produced by the friction of the process causes the base to soften into a paste.

- For small scale production (in the dispensary):
  - Mortar and pestle are used for mixing components
  - Enough heat is produced from the compression to soften the base
  - If much powder is to be incorporated, it is better to warm the mortar
  - The mass is, then, forced into the mold

- For large scale production (Hand or power operated machines are used):
  - Prepare the mass, and place the mass into a cylinder
  - Apply a pressure from one end
  - The mass is forced out of the other end into the suppository molds or die
  - When the die is filled, remove the end plate at the back of the die
  - Apply additional pressure to remove the formed suppository

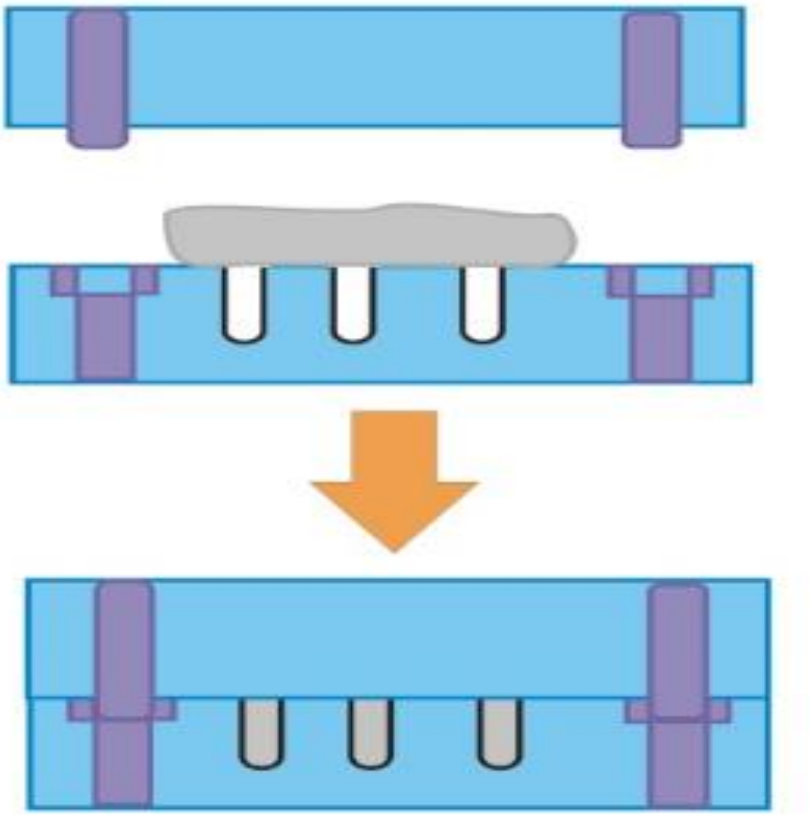


Fig. Suppositories by compression

C. Hand Rolling and Shaping

- An old method
- TBO base is employed in this method.
- A plastic-like mass is formed from the base of grated TBO and other ingredients by severe trituration.
- The mass is rolled into a ball with the palms of the hands.
- Since the suppository base melts near body temperature, before handling it, hands need to be cooled below body temperature by dipping them in ice water.

- The mass is shaped into a cylinder with the help of the spatula.
- The cylinder is cut into appropriate lengths with a knife, each length equal to one suppository.
- The final shaping of the suppository is done with the fingertips

Packaging and Storage of Suppositories

- Glycero-gelatin suppositories are usually packaged in well-closed screw-capped glass containers, preferably at a temperature below 35 °C.
- TBO - based suppositories are usually packaged by wrapping them individually into partitioned boxes to prevent contact and adhesion.
- Most commercially available suppositories are individually wrapped in either foil or polyvinyl chloride (PVC)-polyethylene.
- Since suppositories are sensitive to heat, they should be stored in a cool place, but they should not be frozen.

- Cocoa butter suppositories must be stored below 30°C, preferably in a refrigerator (2 to 8°C).
- Glycerinated gelatin suppositories can be stored at controlled room temperature (20 to 25°C).
- Suppositories are adversely affected by humidity,
  - High humidity causes them to become spongy
  - An extreme dry environment results in the loss of moisture from suppositories, which makes them brittle.

Pessaries

- Pessaries/vaginal suppositories are solid medicated preparations for introduction into the vagina, where they melt or dissolve and exert a local action.

- Pessaries are primarily employed for:

  - **Vaginal infections**, to return the vaginal mucosa to its normal state,

    - For vaginitis

    - Leucorrhoea

  - **Contraception**

- Two types:
  - Moulded pessaries
    - Cone-shaped with rounded up
    - Prepared in a similar way to suppositories
  - Compressed pessaries
    - Made in a variety of shapes: Diamond, Almond, Wedge, Disc or tablet shaped
    - Prepared by compression like tablets

- Most commonly used Pessary base consists combination of the various molecular weight PEGs
  - These are water miscible
  - Sufficiently firm to handle
- Pessaries made from Glycero-Gelatin base need to be heated at 100 ^{o}C for 1 hour
  - To free from pathogens, because the gelatin may be contaminated from its sources
- SAAs and preservatives are commonly incorporated

- Vaginal dosage forms are buffered to acidic pH
  - Vaginal pH is about 4.5
- Pessaries are commonly supplied with insertion devices
  - Avoid contamination
  - Help to insert the Pessary high into the vagina
- Pessaries are to be administered at bed time

Preparation, Packaging and Storage of Pessaries

- Pessaries are prepared by the methods for suppositories, or by compression in a tablet machine.

- Packaging and storage of pessaries is similar to that of suppositories

Labeling requirements for Suppositories and Pessaries:

- 'Store in a cool place'
- 'Not to be taken Orally'
- 'For Rectal/Vaginal use only'
- Patients may be instructed to moisten suppositories or pessaries before insertion
  - To reduce osmotic withdrawal of water from tissues

Important Quality Controls of suppositories/pessaries

- **Appearance**
  - When cut longitudinally and examined with the naked eye - the internal and external surfaces should be uniform
- **Uniformity of weight**
  - Weigh 20 suppositories individually
  - No suppository must deviate from the average by more than 5%
  - Two may deviate by not more than 7.5%

- **Disintegration**
  - Disintegrating apparatus is used
  - Disintegration is evidenced by:
    - Complete solution, except insoluble powder
    - Disintegration products that are small enough to sink through the perforation, or
    - Complete melting of the solid matter

NB. No solid core should be detectable.

Other Rectal and Vaginal preparations

- Assignment to be submitted:
  - Read on the different forms of Rectal, Vaginal and Urethral Dosage Forms, and submit a note of not more than 3 pages.
    - Tablets And Capsules
    - Ointments, Creams, and Aerosol Foams
    - Gels and Jellies
    - Contraceptive Sponges
    - Intrauterine Devices
    - Powders
    - Solutions (Vaginal Douches, Retention Enemas, and Evacuation Enemas)